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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,707	10/15/2004	Tsuyoshi Shimoboji	09857/0201259-US0	6749

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EXAMINER	
OLSON, ERIC	

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1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,707	SHIMOBOJI, TSUYOSHI	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 20, 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-10,12,13,16,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7,8,10,12,13,16,17,20 and 21* is/are rejected.

7)☒ Claim(s) *3,4 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted November 20, 2007 wherein claims 1, 3-5, 10, 12, 13, and 20 are amended and claims 6, 11, 14, 15, 18, 19, 22, and 23 are cancelled. This application is a national stage application of PCT/JP03/04949, filed April 18, 2003, which claims priority to foreign applications JP2002-116508, filed April 18, 2002, JP2002-209429, filed July 18, 2002, and JP2002-331551, filed November 15, 2002.

Claims 1-5, 7-10, 12, 13, 16, 17, 20, and 21 are pending in this application.

Claims 1-5, 7-10, 12, 13, 16, 17, 20, and 21 as amended are examined on the merits herein.

Applicant's amendment, submitted November 20, 2007, with respect to the rejection of instant claims 1-13, 16, 20, and 21 under 35 USC 112, second paragraph, for being indefinite for failing to indicate whether the association of the hyaluronic acid with the block copolymer is covalent or noncovalent, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to indicate a covalent association. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 20, 2007, with respect to the rejection of instant claims 3-4 under 35 USC 112, second paragraph, for being indefinite for failing to indicate whether it is the block copolymer, the hyaluronic acid, or both, that is bound at only one end, has been fully considered and found to be persuasive to

remove the rejection as the claims have been amended to indicate that this limitation applies to the block polymer and not to the hyaluronic acid. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 20, 2007, with respect to the rejection of instant claim 10 under 35 USC 112, second paragraph, for being indefinite for failing to indicate what is meant by the phrase, "its main component", has been fully considered and found to be persuasive to remove the rejection as the claim has been amended to state that the product is **an active ingredient** instead. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 20, 2007, with respect to the rejection of instant claim 13 under 35 USC 112, second paragraph, for being indefinite for failing to indicate what is meant by the phrase, "in the form of an injection", has been fully considered and found to be persuasive to remove the rejection as the claim has been amended to state that the product is injectable instead. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 20, 2007, with respect to the rejection of instant claims 11 and 13 under 35 USC 112, first paragraph, for lacking enablement for treating any joint disease whatsoever, has been fully considered and

found to be persuasive to remove the rejection as claim 11 is cancelled and claim 13 now depends form the fully enabled claim 12. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 20, 2007, with respect to the rejection of instant claims 1-4, 6, 7, 9-13, 16, 17, 20, and 21 under 35 USC 103(a) for being obvious over Rhee et al. in view Schmolka et al., has been fully considered and found to be persuasive to remove the rejection as the cited prior art gives no guidance to prepare the specific product that is claimed in the instant claims, having the specific phase transition temperature recited in the amended claims. Therefore the rejection is withdrawn.

Applicant's amendment, submitted November 20, 2007, with respect to the rejection of instant claims 1-4, 7-13, 16, 17, 20, and 21 under 35 USC 103(a) for being obvious over Spaltro et al. in view Schmolka et al., has been fully considered and found to be persuasive to remove the rejection as the cited prior art gives no guidance to prepare the specific product that is claimed in the instant claims, having the specific phase transition temperature recited in the amended claims. Therefore the rejection is withdrawn.

Claim Objections

Claims 3-4 are objected to because of the following informalities: The claims recite the phrase, "at one of its two ends of said block polymer." This phrase is

grammatically incorrect. The correct syntax is, "at one of **the** two ends of said block polymer." Appropriate correction is required.

Claim 13 is objected to because of the following informalities: the phrase, "which is in the form suitable to be filled in a syringe," is grammatically incorrect. The correct phrase is, "which is in **a** form suitable to be filled in a syringe." Appropriate correction is required.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 5, 7, 8, 10, 12, 13, 16, 17, 20, and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Kim et al. (Reference included with PTO-1449, also note that Kim et al. was first available online on February 3, 2002, as evidenced by the printout of the online citation included with the PTO-892) Kim et al. discloses a composite hyaluronic acid/Pluronic hydrogel made by covalently attaching hyaluronic acid to a polyethylene oxide / polypropylene oxide / polyethylene oxide (PEO/PPO/PEO) triblock copolymer by the carboxyl groups of HA. (p. 70, left column, last paragraph) The pluronic polymer is added at a 15:1 ratio by weight to the hyaluronic acid, leading to a ratio of much more than 8 mol %. (p. 71, left column, third paragraph)

Note that the technical bulletin for Pluronic F127 (included with PTO-892) indicates that this polymer has an average molecular weight of 12.6 kD. Therefore, a 15% composition of pluronic contains 150 mg/mL, or ~1.2 µmol/mL of polymers. Since the polymer used is activated at both ends, the composition contains ~2.4 µmol/mL of polymer ends. The composition also contains 1%, or 10 mg/mL of hyaluronic acid, containing ~26 µmol/mL of carboxyl groups. Therefore, about 9% of the carboxyl groups are substituted by polymer, fulfilling the limitation of over 8% of the groups being substituted. The conjugated polymer formed a gel that underwent a phase transition at 20° in a 10% solution, with local micellization significantly altering the swelling ratio. (p. 73, right column, also Fig. 2) The gel prepared by Kim et al. is reasonably considered to be useful in for treating joint disease, assisting or treating surgical operations, and repairing tissue, thus fulfilling the limitations of claims 11, 12, 16, 17, 20, and 21. It is also reasonably considered to be in the form of an injection according to instant claim 13 as it is capable of being injected. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Furthermore, either the gel itself or the rHGH drug delivery system disclosed on p. 71, right column, third paragraph can be considered to be a pharmaceutical preparation according to instant claim 10, and the

gel is an active agent because it is suitable for use in various therapeutic methods such as those recited in the instant specification.

For these reasons, Kim et al. anticipates the claimed invention.

Response to Argument: Applicant's arguments, submitted November 20, 2007, with respect to the above grounds of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Kim does not anticipate claim 6, and therefore the limitation of claim 6 incorporated into claim 1 serves to distinguish the instant claims from Kim et al. However, the non-inclusion of claim 6 in the listing of anticipated claims was an error as can clearly be seen by the fact that the above grounds of rejection include a mention of the fact that the gel of Kim et al. undergoes a phase transition at 20C in 10% solution with a dramatic change in swelling behavior due to changes in the micellization behavior. This change is reasonably considered to be a phase transition. Therefore the rejection is maintained.

Conclusion

Claims 1, 2, 5, 7, 8, 10, 12, 13, 16, 17, 20, and 21 are rejected. Claims 3, 4, and 9 are objected to for depending from a rejected base claim but would be acceptable if rewritten in independent form incorporating all the limitations of the rejected base claim and any intervening claims. Reasons for indication of non-rejected subject matter are as follows:

Claims 3, 4, and 9 are directed to compositions that are fully described and enabled by Applicant's specification as originally filed. For example, pp. 7-12 of the

specification, under the heading "best modes for carrying out the invention" describe the claimed limitations of this hyaluronic acid product. Pp. 13-16 describe a method for making the composition, and pp. 17-19 describe and enable several medical uses for the gel composition. Therefore the claimed invention meets the requirement of 35 USC 112.

Furthermore, the claimed invention is seen to be novel and non-obvious over the prior art. Although Rhee et al. and Spaltro et al. both describe hyaluronic acid covalently bonded to a PPO-PEO block copolymer, and Pluronic triblock copolymers such as those used in the claimed invention were known in the prior art, for example Schmolka et al., one of ordinary skill in the art would not have been motivated to produce the specific claimed invention. While the claimed gel is in fact included within the broad disclosure of Rhee et al. or Spaltro et al., producing it would require the specific optimization of multiple parameters, such as the length of the two polymers, the specific triblock polymer used, and the relative amounts of hyaluronic acid and pluronic. Achieving a specific phase transition temperature between 20-35 degrees Celsius would require one of ordinary skill in the art to optimize multiple parameters within the broad disclosure of the prior art. However, Rhee et al. and Spaltro et al. do not mention phase transition temperature as an important variable to be optimized by one of ordinary skill in the art, so one of ordinary skill in the art would have no reason to optimize the phase transitions temperature. Furthermore, Rhee et al. proposes that the polymers be crosslinked *in vivo* after injection as a liquid. (column 26, lines 42-58) This method of injection followed by crosslinking implies that the crosslinked gel is a solid at

room temperature, and would be completely unnecessary if the gels could be injected as a room temperature liquid and then undergo the phase transition upon warming *in vivo*.

Furthermore, with regard to Kim et al., while the disclosed compositions of Kim et al. do in fact undergo a phase transition around 20 degrees, they lack other elements of the claims. In particular, the pluronic polymers of Kim et al. crosslink the hyaluronic acid by being attached to hyaluronic acid at both ends, as illustrated by the figure 3 on p. 74 of Kim et al. In addition, the hyaluronic acid used to make these gels is larger than that recited in claim 9. p. 70, section 2.2 of Kim et al. discloses that 500 mg, or $2.85x10^{-4}$ mmol, of hyaluronic acid is used. From these figures it can be calculated that the average molecular weight of the hyaluronic acid is about 1750000 daltons, which is more than the limit of 1500000 daltons or less recited in claim 9. One of ordinary skill in the art would not have had any reason to substitute lower molecular weight hyaluronic acids for those used by Kim et al.

Therefore for these reasons, the claimed invention is seen to satisfy the requirements of 35 USC 112, 102, and 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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